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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,457	06/12/2001	James Pan	P2871R1	5233

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,457	PAN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-48* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Status of Application, Amendments and/or Claims

The information disclosure statement filed 16 June 2003 (Paper No. 13) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The amendment filed 16 June 2003 (Paper No. 15) has been entered in full. Claims 1-18 are under examination.

The Formal Drawings were received.

Applicants do not contest the Examiner's priority finding reported in the previous Office Action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The objection to the drawings for failing to comply with 37 CFR 1.84(p)(5) as set forth at pages 3-4 of the previous Office Action (16 December, Paper No. 12) is *withdrawn* in view of Applicants' argument (16 June 2003, Paper No. 15).

The objection to claims 1-9, 11 and 15 as set forth at page 4 of the previous Office Action (16 December, Paper No. 12) is *withdrawn* in view of the amendment (16 June 2003, Paper No. 15).

The rejection of claims 6-10 and 12 under 35 USC 112, second paragraph as set forth at pages 4-5 of the previous Office Action (16 December, Paper No. 12) is *withdrawn* in view of the amendment (16 June 2003, Paper No. 15).

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection is set forth at pages 4-5 of the previous Office Action (16 December, Paper No. 12). Applicants' arguments have been fully considered but not deemed persuasive because the instant claim does not have a recitation of clear hybridization conditions.

Claim Rejections - 35 USC § 101

Claims 1-18 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. The basis for this rejection is set forth at pages 5-6 of the previous Office Action (16 December, Paper No. 12).

Applicants have stated that while Example 11 is a prophetic example describing how the polypeptides of the invention can be tested in a transgenic animal model, the data and the particular NS4 gene used to make the transgenic animal is reported in the description of Figures 3A-3C at page 11, lines 6-8. Applicants have stated that the reduction in body weight in combination with increased lean body muscle mass is an observed effect seen in transgenic animals expressing DNA146649-1789R1 (SEQ ID NO:1). Applicants contend that the critical conclusion is the relative effect that transgenic mice that express NS4 v. control mice that do not.

Applicants' arguments have been fully considered but not deemed persuasive. There is not a clear nexus between the effect in the mouse and the claimed polynucleotide/polypeptide. Contrary to Applicants' assertion more information is needed than transgenic mice that express the cDNA of NS4 have lower total weight/fat or increased lean muscle. The utility of the claimed invention relies on the function of the encoded gene product. It is not clear what the expressed protein is doing once expressed. The specification states that the instant invention has utility for body weight disorders but fails to disclose working models which demonstrate that the expressed protein could be employed for therapeutic purposes in the treatment of weight disorders (ex. administering the protein to obese animal models). Furthermore, the transgenic mouse is experiencing the effect of the protein from its conception. It is unclear if the protein is exerting its effect during embryogenesis or at other times during development. Thus, there is no indication that administering the protein to an adult, for instance an obese patient, would have any effect. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 1-18 are also rejected under 35 U.S.C. 112, first paragraph, enablement. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth at pages 7-9 of the previous Office Action

(16 December, Paper No. 12). Applicants incorporate their response to the rejection under 35 USC 101 in response to the rejection under 35 USC 112, first paragraph. Applicants' arguments have been fully considered but are not found to persuasive for the reasons discussed above in the maintained rejection in 35 USC 101.

In addition, claims 1-7, 11-14, 16-18 are not enabled for sequence variants and fragments. Applicants state that the preparation of NS4 variants is described in the specification. Applicants cite page 40, line 19-page 44, line 21 and page 44, line 23-page 50, line 18. Applicants state that the functional assay to determine NS4 biological activity is the transgenic model described in Example 11. Applicants submit Bowie *et al.*, in support of their argument that polypeptide function is largely tolerant to residue primary structure residue substitutions.

Applicants' arguments have been fully considered but not deemed persuasive. The specification provides no working example of any variant sequence which would be within the claims. As was stated in the last Office Action, it is in no way predictable that randomly selected mutations, deletions, etc. in the disclosed sequence would afford a protein having activity comparable to the one disclosed.

Bowie *et al.* does not fully state that polypeptide function is largely tolerant to residue primary structure residue substitution. For example in the lac repressor, Bowie *et al.* contend that at some positions, no substitutions or only conservative substitutions were allowed (page 1306, 3rd paragraph). Bowie *et al.* state that to carry out their function, these catalytic residues and binding residues must be precisely oriented in three dimensions. Consequently, mutations in residues that are required for structure

formation or stability can also have dramatic effects on activity (page 1306, 4th paragraph). Bowie *et al.* assert that functionally important residues should be conserved in sets of active sequences, but it is not possible to decide whether a side chain is functionally or structurally important just because it is invariant or conserved. To make this distinction requires an independent assay of protein folding (page 1308, 3rd paragraph). In addition, Bowie *et al.* state that it is often difficult to align sequences as the level of sequence similarity decreases and it is sometimes impossible to detect statistically significant sequence similarity between distantly related proteins (page 1308, 4th paragraph).

Applicants cite case law to apply in the present context. Applicants state that through the transgenic animal model, they have disclosed how the function of such variants can be tested. In relating to the Wands factors, Applicants contend that the preparation of transgenic animal is not difficult, directions for the exact preparation in the present context is provided in the Example 11, the nature of the invention is a polypeptide and functional variants thereof, a claim type and scope that is limited, reasonable and now almost routine in the domain of patent law, the state of the prior art and the relative skill of those in the art is well advanced and the predictability of the polypeptide creation and expression, as well as the preparation of transgenic animals is very well characterized and known.

Applicants' arguments have been fully considered but not deemed persuasive. The Examiner has cited references in this Office Action in reply to Applicants' argument to demonstrate the art at the time of filing. The transgenic art taught that expression of

a transgene was unpredictable because of poor expression of the transgene due to the insertion site of the transgene into the genome. Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron (1997) Molec. Biotech., page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron (1997), Molec. Biotech., page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron (1997), Molec. Biotech., page 256, lines 10-13). Further, Sigmund (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund (2000) Arteroscler. Throm. Vasc. Biol., page 1426, col. 1, parag. 1, lines 1-7).

If one skilled in the art can readily anticipate the effect, than there is predictability in the art. In this case, however, the art is unpredictable based on the evidence provided. The evidence for the degree of predictability in the art also relates to the amount of direction needed in the specification. The instant claims encompass sequence variants. Without sufficient guidance, the changes which can be made in the structure and still maintain sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. A considerable amount of time is permissible for the quantity of experimentation needed

to make or use the invention based on the disclosure. However this depends on if the invention is routine or if the skilled artisan is given sufficient direction or guidance. In the instant case, the experimentation is not routine and Applicant has provided little or no guidance. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

Claims 1-7, 11-14, 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pages 9-10 of the previous Office Action (16 December, Paper No. 12).

Applicants discuss Vas-Cath v. Mahurkar and In re Wertheim. Applicants state the burden of showing that the claimed invention is not described in the specification rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not in ipsis verbis is insufficient. Applicants state that the determination is factual and depends on the nature of the invention and amount of knowledge imparted to those skilled in the art by the disclosure. Applicants content that the Examiner's reliance on Vas-Cath in support of the rejection for a lack of written description is misplaced and that the cases support Applicants' position that the specification does in fact teach an adequate written description. Applicants discuss Fiers v. Sugano, Amgen

v. Chugai, and Fiddes v. Baird. Applicants contend that the Examiner appears to be relying upon Amgen in support of the above rejection because written description is essentially an issue of possession, or whether or not Applicants have clearly distinguished the invention from the prior art and have thereby demonstrated possession of the invention. Applicants assert that the Examiner's reliance upon Fiers, Amgen and Fiddes is misplaced. Applicants maintain that they do describe nucleic acid encoding SEQ ID NO:1, have both structural (% sequence identity) and functional (transgenic animal phenotype) limitations defining the present claims scope. Lastly, Applicants contend that the present claims contain both a narrowly focused structural limitation of 80% sequence identity to SEQ ID NO:1 coupled with the functional limitation of (1) lower relative weight, (2) lower fat/total body weight ratio, and (3) greater lean muscle mass/total body weight ration.

Applicants' arguments have been fully considered but not deemed persuasive. Contrary to Applicants' assertion, the PTO has showed that the claimed invention is not described in the specification and has given reasons why the instant description lacks support. The instant claims encompass gene sequences, sequences that hybridize to SEQ ID NO:1, the DNA encoding SEQ ID NO:4, corresponding sequences from other species, mutated sequences, allelic variants, splice variants, fragments, sequences that have a recited degree of identity (similarity, homology), and so forth. There is substantial variability among the species of DNAs encompassed within the scope of the claims that is not described. The instant claims encompass genes yet to be discovered. There is no disclosure regarding the coding capacity of any of the variants/fragments

cited. Defining the variants/fragment in functional terms would not suffice in the absence of a disclosure of structural features or elements of a cDNA that would encode a protein having a stated function. Furthermore, Applicants have not expressed any of the variant cDNAs to discern the function. The specification states that these types of changes are routinely done in the art and provides a table of potential amino acid substitutions. The specification, however, does not provide any guidance as to what changes should be made. There is no description of variants of SEQ ID NO:1 that exist, while still maintaining function. Specific, not general guidance is what is needed. The disclosure fails to describe the common attributes or characteristics that identify the members of the genus, and because the genus is variant, SEQ ID NO:1 alone is insufficient to describe the genes. The disclosure fails to provide a representative number of species to describe the genus. Applicants state that the determination is factual and depends on the nature of the invention and amount of knowledge imparted to those skilled in the art by the disclosure. As was stated in the enablement rejection, several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

RMD

RMD
September 11, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER